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Abstract: Depression has repeatedly been linked to subclinical hypothyroidism, and thyroid hormones have successfully been used to augment antidepressant treatment. By contrast, the extent of thyroid dysfunction in anxiety disorders remains less clear. This is surprising, given that anxiety-related symptoms (e.g., nervousness, palpitations, increased perspiration) are highly prevalent in hyperthyroidism. The present study was undertaken to synthesize the literature on hypothalamic-pituitary-thyroid (HPT) axis functioning in anxiety disorders. The PubMed and PsycINFO databases were systematically searched. Three types of studies were included: (1) "comorbidity studies" assessing the prevalence of thyroid disorders in individuals with anxiety disorders, (2) "case-control studies" comparing HPT parameters between patients and controls, and (3) "correlational studies" assessing self-reported anxiety levels and HPT parameters. Risk of bias was assessed via a standardized quality rating. Twenty studies were eligible. Nearly all found the comorbidity between anxiety and thyroid disorders was significant. Half of the studies additionally supported the notion of subtle thyroid dysfunction in that thyroid-stimulating hormone (TSH) responses to the administration of thyrotropin-releasing hormone (TRH) were blunted and an inverse relationship was observed between self-reported anxiety levels and TSH. Overall, HPT assessments were well conducted, but several studies failed to adjust their analyses for smoking, body mass index (BMI), and depression. The findings resonate well with clinical recommendations to routinely screen for thyroid disorders in patients with anxiety disorders, and with what is known from basic research about thyroid-brain interactions. The results of the risk of bias assessment underscore the importance of further high-quality experimental and longitudinal epidemiological research.

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Hypothalamic-pituitary-thyroid (HPT) axis functioning in anxiety disorders. A systematic review

Short title: Thyroid functioning in anxiety

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Abstract

Background

Depression has repeatedly been linked to subclinical hypothyroidism, and thyroid hormones have successfully been used to augment antidepressant treatment. By contrast, the extent of thyroid dysfunction in anxiety disorders remains less clear. This is surprising, given that anxiety-related symptoms (e.g., nervousness, palpitations, increased perspiration) are highly prevalent in hyperthyroidism. The present study was undertaken to synthesise the literature on hypothalamic-pituitary-thyroid (HPT) axis functioning in anxiety disorders.

Methods

The PubMed and PsycINFO databases were systematically searched. Three types of studies were included: 1) "comorbidity studies" assessing the prevalence of thyroid disorders in individuals with anxiety disorders, 2) "case-control studies" comparing HPT parameters between patients and controls, and 3) "correlational studies" assessing self-reported anxiety levels and HPT parameters. Risk of bias was assessed via a standardised quality rating.

Results

Twenty studies were eligible. Nearly all found the comorbidity between anxiety and thyroid disorders was significant. Half of the studies additionally supported the notion of subtle thyroid dysfunction in that thyroid-stimulating hormone (TSH) responses to the administration of thyrotropin-releasing hormone (TRH) were blunted and an inverse relationship was observed between self-reported anxiety levels and TSH. Overall, HPT assessments were well-conducted, but several studies failed to adjust their analyses for smoking, BMI, and depression.

Conclusions

The findings resonate well with clinical recommendations to routinely screen for thyroid disorders in patients with anxiety disorders, and with what is known from basic research about thyroid-brain interactions. The results of the risk of bias assessment underscore the importance of further high-quality experimental and longitudinal epidemiological research.

Keywords: Anxiety; hypothalamic-pituitary-thyroid axis; Graves' disease; Hashimoto's thyroiditis; panic disorder; phobia

Introduction

For decades, the hypothalamic-pituitary-thyroid (HPT) axis has been subject to investigation in depressive disorders (Fountoulakis et al., 2006). An impetus for this line of research to evolve was that patients with overt hypothyroidism exhibit symptoms that overlap with those of major depression (Feldman, Shrestha, & Hennessey, 2013). This is not surprising, given the widespread expression of thyroid hormone receptors in almost all bodily tissues, including the brain (Bauer, Goetz, Glenn, & Whybrow, 2008). Subsequent research has revealed that, conversely, some patients with depressive disorders seem to be characterised by subclinical forms of hypothyroidism (Fountoulakis et al., 2006). Correspondingly, triiodothyronine (T3) has successfully been used as an augmentation strategy in depressed patients who were resistant to standard first line treatments, such as antidepressants (Cleare et al., 2015).

By contrast, far less research has been dedicated to studying HPT functioning in anxiety disorders. As with depression, some of the most important anxiety symptoms are mimicked by thyroid disorders. For instance, patients with overt hyperthyroidism frequently report anxiety, fatigue, poor concentration, and disturbed sleep, all of which constitute core symptoms of generalised anxiety disorder (GAD; De Leo, Lee, & Braverman, 2016). In addition, a number of somatic symptoms, such as palpitations, shortness of breath, and increased perspiration overlap with what patients with panic disorder (PD) experience during panic attacks. The reverse, namely the extent of thyroid dysfunction as present in patients with anxiety disorders, however, still remains unclear. Learning more about such dysfunction would first mean to obtain an estimate of the presence of (subclinical) thyroid disorders in patients with anxiety disorders. Second, it would imply to study subtle alterations in individual HPT parameters, i.e., thyrotropin releasing hormone (TRH), thyroid-stimulating hormone (TSH), and the thyroid hormones T3, and thyroxine (T4), as has been done in depression. Doing so may shed light on the intricate relationship between anxiety and HPT functioning and could help to determine whether the above listed anxiety symptoms may emerge as an epiphenomenon of subclinical thyroid dysfunction, too.

In their narrative review of this literature, Simon et al. (2002) found initial support for an increased prevalence of thyroid disorders in patients with GAD and PD. However, as noted by the

authors, at the time when their review was published, no community or primary care studies were yet available, and the authors therefore had to rely on a number of relatively small secondary and tertiary care studies, which likely suffered from selection bias. In addition, sufficiently sensitive kits to determine TSH were only developed between 1980 and 1990, which may have rendered it impossible for some of the included studies to detect subclinical thyroid dysfunction (nine of the 13 included studies were published before 1990). Finally, very few data on subtle alterations in the HPT axis were available, which may be gained from studies comparing patients' resting or stimulated thyroid parameters with those of healthy controls.

The present study was therefore undertaken to update and extend this previous review by systematically searching and synthesising the literature on HPT functioning in anxiety disorders. Our specific aims were threefold: 1) to investigate whether patients with anxiety disorders have an increased risk of (subclinical) thyroid disorders, 2) to find out whether the same patients are characterised by subtle alterations in thyroid parameters when compared to controls, and 3) to determine whether there is a continuous relationship between anxiety levels and thyroid parameters. Based on their symptom profiles and on the previous literature review by Simon et al. (2002), we mainly expected studies using patients with GAD, PD, and social anxiety disorder (SAD) to have investigated and revealed abnormalities in HPT functioning.

Methods

Search strategy

Potentially relevant records were identified by systematically searching the PubMed and PsycINFO databases from 1990 until February 2017. Key words and subject headings were selected in accordance with the thesaurus of each database. The search string consisted of two components: 1) "anxiety disorder", including synonyms and related terms and 2) "thyroid" and synonyms and related terms. Both searches were confined to studies conducted in humans. No language restrictions were applied, but one study was later excluded because it was written in Russian.

Screening and study selection procedure

Three types of studies were to be included. The first type were “comorbidity studies” assessing the prevalence of thyroid disorders in individuals with anxiety disorders and/or their comorbidity in apparently healthy individuals of the general population. The second type were “case-control studies” comparing HPT parameters between patients with anxiety disorders and patients with other mental disorders or healthy controls. Anxiety disorders comprised all categories contained in the relevant DSM-5 chapter (APA, 2013) and applying to adults, namely specific phobia, SAD, PD, agoraphobia, and GAD, and had to be diagnosed according to DSM-III-R (APA, 1987), DSM-IV (APA, 2000), DSM-5 (APA, 2013), or ICD-10 criteria (WHO, 1992). The third type were “correlational studies” assessing self-reported anxiety levels (using a validated questionnaire) and HPT parameters in patients with any of the above anxiety disorders or in apparently healthy individuals of the general population. Abiding by these inclusionary criteria meant that studies confined to specific populations (e.g., pregnant women) were excluded, and so were studies exclusively looking at patients with obsessive-compulsive disorder or posttraumatic stress disorder. Comorbidity with mental or somatic illnesses, however, was allowed, and so was the current intake of medication, but this was recorded. Full-text articles were retrieved and checked for relevant results. The reference sections of all articles were manually searched for additional records.

Data extraction

For each identified study, two members of the study team collected information about the authors, year of publication, the sample and setting, eligibility criteria, diagnostic procedures for the anxiety disorder, measurement of self-reported anxiety levels, diagnostic procedures for thyroid disorders, assessment of thyroid parameters, and the main study results.

Risk of bias was assessed by means of a modified version of a quality rating scale that was first used in a meta-analysis on cortisol in functional somatic syndromes (Tak et al., 2011) and on cortisol in predicting treatment response in anxiety and depressive disorders (Fischer & Cleare, 2017; Fischer, Strawbridge, Vives, & Cleare, 2017). We adapted five of the original items (some were excluded due to non-applicability) to match the present research question and scored them using the original three-point scale (0-2). The complete checklist can be found in Table 1. Depending on whether a control group was included in the study or not, the maximum attainable quality score was between 8 and 10.

- Insert Table 1 here -

Results

Search results

The search yielded 1594 records, of which 38 were considered potentially relevant for the present research question based on their title or abstract. Of these, 18 studies were excluded due to the following reasons: they were not conducted in patients with a primary diagnosis of an anxiety disorder, did not diagnose anxiety disorders in accordance with DSM or ICD criteria, were single-case studies, did not assess thyroid functioning, or did not report relevant results. In total, 20 studies were eligible for data extraction.

Study characteristics

Tables 2-4 show the characteristics of all 20 included studies. Ten studies evaluated how frequently thyroid disorders were present in patients with anxiety disorders (comorbidity studies), nine compared thyroid parameters between patients with anxiety disorders and controls (case-control studies) and seven correlated self-reported anxiety levels with thyroid parameters (correlational studies). More detailed study characteristics are provided in the corresponding sections below.

- Insert Tables 2-4 here -

Risk of bias

Depending on whether a control group was included in the study or not, the maximum attainable quality score was between 8 and 10. The average score was 3±1 (standard deviation; SD) for studies with a maximum score of 8 (range: 2-5) and 5±2 for studies with a maximum score of 10 (range: 3-8). This difference in means was mainly due to the fact that almost all of the latter studies scored points on the extra item for carefully selecting their control group. Across all studies, the highest scores were obtained for how hormonal assessments of the HPT axis were conducted, including the diagnostic

procedures for establishing thyroid disorders as well as the handling of samples to determine thyroid parameters (item 3). By contrast, only one study reported whether the assessors of anxiety were blind to thyroid status (item 4) and many studies failed to adjust their statistical analyses for relevant trait-like confounders (item 5). More specifically, only two studies controlled for smoking, three for BMI and eight for depression. Age and sex, by contrast, were controlled for by the majority of studies.

Comorbidity studies: thyroid disorders in patients with anxiety disorders

Ten studies in total contained comorbidity analyses (see Table 2), using samples from the USA, South America, Europe, and Australia. Of these, four were conducted in community samples while the other six used outpatients. All four *community studies* found significant relationships between the presence of anxiety disorders and the presence of thyroid disorders, the latter established by questionnaires, medical interviews, physical examination, and/or laboratory testing. However, one of these studies later failed to replicate their positive finding in an independent sample of slightly older adults (Witthauer et al., 2016). All six *outpatient studies* mainly included patients with PD. The prevalence of any thyroid disorder in these patients ranged from 2.2% to 39.3%, with some studies relying on medical histories to obtain diagnoses and others measuring thyroid parameters and using cut-off values. Two of these studies compared patients with different types of anxiety disorders with each other. Both found that patients with GAD had the highest prevalence of comorbid thyroid disorders. Unfortunately, none of the comorbidity studies separated results into subclinical and overt forms of thyroid disorders. While most studies did not report which thyroid disorders they assessed, one study found hypothyroidism to be more common in PD (Gloger, Fardella, Santis, & Bitran, 1997), while another showed hyperthyroidism to prevail in the same patients (Fardella et al., 2000).

Case-control studies: thyroid parameters in patients with anxiety disorders and controls

Nine studies included case-control comparisons (see Table 3). These studies were conducted in the US, South America, and Europe. Most studies exclusively used outpatients with PD and all excluded patients with a history of thyroid disorders or any current somatic disease (including overt thyroid disorders). In terms of *resting* HPT parameters, none of the studies found any differences in cerebrospinal TRH, plasma/serum TSH, T3, free T4, or T4 when contrasting patients with healthy

controls. One study compared patients with PD to patients with depressive disorders and found that the former group had higher fT4 levels (Fardella et al., 2000). A more complex picture emerged when focusing on *stimulated* thyroid parameters, in this case TSH after a 400-500 µg TRH challenge. These challenges were conducted to test the integrity of the HPT axis, and most authors expected attenuated responses based on previous findings in depressed patients. Of the four studies, two indeed showed blunted responses in patients when compared to healthy controls, while the other two could not detect any differences (continuous analyses). When separating patients and controls into normal vs. abnormal responders (cut-off of 5 µU/ml or 7 µU/ml), again two out of the four studies found that patients more often fell into the abnormal responder category. Overall, three of the four studies reported some evidence for attenuated TSH responses in anxious patients, be it based on continuous or categorical analyses.

Correlational studies: self-reported anxiety levels and thyroid parameters

Seven studies correlated self-reported anxiety levels with thyroid parameters (see Table 4). These studies were conducted in the USA, Europe, and Japan. The settings included general population based samples, primary care samples, outpatient and inpatient samples. The one *general population based sample* split participants into those with vs. without current T4 intake and found a positive relationship between TSH and anxiety levels in medicated and a negative relationship in unmedicated individuals (Panicker et al., 2009). The latter finding was confirmed in a large *primary care sample* of older patients (Roberts et al., 2006), while an earlier study in a similar setting and using a small sample of younger females had failed to find such a link (Balada, Torrubia, & Arque, 1992). Two of the four *clinical studies* showed no dose-response relationship between resting or stimulated thyroid parameters and anxiety levels, while the other two showed a negative association between THR stimulated TSH, resting fT4 and anxiety levels in patients with PD.

Discussion

The aim of this systematic review was to investigate the extent to which patients with anxiety disorders are affected by thyroid dysfunction. We report three main findings: First, patients with an anxiety disorder were significantly more likely to concomitantly have a thyroid disorder. Second, patients with

PD and SAD did not differ from healthy controls in resting thyroid parameters, but half of the studies found evidence for attenuated TSH responses upon stimulation with TRH. Third, there was evidence for a negative relationship between self-reported anxiety and TSH levels.

The first finding is in line with the first and only available review of the literature that was published 15 years ago (Simon et al., 2002), and extends it by providing evidence for comorbidity between anxiety and thyroid disorders in two different types of samples: population-based and clinical. This implies that the increased comorbidity cannot simply be attributed to selection bias, as may occur in treatment-seeking individuals, and thus increases the generalisability of this finding. Further adding to its robustness, the included studies greatly varied in how they assessed thyroid disorders, such as for example in their use of cut-off values for TSH, T3, T4, and/or antibodies, but still yielded conclusive results. This heterogeneity reflects ongoing controversies about the reference ranges for thyroid dysfunction and the general lack of consent in terms of diagnostic procedures (Chaker, Bianco, Jonklaas, & Peeters, 2017; De Leo et al., 2016). Notably, the nature (hypothyroidism vs. hyperthyroidism) and severity (subclinical vs. overt) of the comorbid thyroid disorders remains unclear, as barely any of the studies reported this. Moreover, there is a possibility that part of the observed comorbidity is due to the simultaneous presence of mood disorders, which were not always excluded or adjusted for. This is supported by the extremely high co-occurrence of GAD and mood disorders, which during the preparation of DSM-5 even led to suggestions of creating a category combining the two disorders (Goldberg et al., 2010). Finally, none of the studies was longitudinal, which means that the temporal order of this relationship could not be established. This is especially problematic seeing that cross-sectional research also shows that individuals with thyroid disorders have an increased probability of a concomitant anxiety disorder (e.g., Giynas Ayhan et al., 2014; Patten, Williams, Esposito, & Beck, 2006). However, in the study of Sareen et al. (2006) and Witthauer et al. (2016), using age-of-onset data, anxiety disorders were shown to precede the onset of thyroid disorders in the majority of cases, which could mean that subtle HPT axis alterations in anxious patients over time progress into subclinical and/or overt forms of thyroid disorders.

Further support for this notion may be gained from studies comparing HPT axis functioning between anxious patients and healthy controls – both free of any overt thyroid conditions. According to the present review, there is no difference in any resting HPT axis parameter between the two groups.

This null-finding could either reflect real absence of subtle basal abnormalities in patients or be the due to methodological problems with single time point measurements, which are more susceptible to the influence of state-like confounders. For instance, thyroid parameters are known to follow specific circannual and circadian rhythms (Kim et al., 2013; Russell et al., 2008). Invariant sampling across seasons could thus have masked small group effects. By contrast, the fact that the null-finding was unanimous across studies with and without standardisation of sampling schedules renders it unlikely for time of day to have superimposed group effects.

Results regarding stimulated TSH were equivocal, with half of the studies showing blunted responses to TRH challenge in anxious patients. All stimulation studies were remarkably homogeneous in the size of their sample and in their selection of patients: All used subjects in their mid-thirties, around half of which were women, and none of which had an overt thyroid disorder, were depressed, or currently using medication. There was more heterogeneity in terms of TRH administration and type of assay used, but none of these factors could explain the discrepant findings either. However, three out of four studies found some evidence for diminished TSH responses, either in continuous (peak TSH) or categorical (TRH non-responders vs. responders) analyses. One way to make sense of this is that an interaction of unreported patient characteristics (e.g., BMI) with specifics of the TRH test protocol (e.g., dosage) accounted for the observed inconsistencies. The finding of altered HPT functioning in PD and SAD aligns well with current knowledge about structural and functional thyroid-brain interactions. These include the presence of thyroid hormone receptors in various areas of the limbic system and cross-communication of the central thyroid, noradrenergic and serotonergic systems (Bauer et al., 2008). The molecular mechanisms underlying these connections and their potential role in contributing to anxiety-related symptoms merits further research, should the here reported evidence for subtle dynamic changes in the HPT axis be replicated. Notably, in those patients with (subclinical) hyperthyroidism, a diminished TSH response could suggest already existent stimulation of the pituitary by the hypothalamus, whereas in (subclinical) hypothyroidism, a diminished TSH response could suggest pituitary dysfunction.

Finally, a negative association between self-reported anxiety levels and TSH emerged in two very large samples of the general population. This mirrors the first finding of significant comorbidity between anxiety disorders and thyroid disorders on a subclinical level. The results from patient

samples, however, were inconclusive and need to be interpreted with caution, since they were often reported as part of a secondary analysis and most studies failed to adjust these for relevant confounders (hence the low quality assessment scores).

There are different explanations for what may reside at the core of the co-occurrence between anxiety and alterations in the HPT axis. It is possible that the observed comorbidity is a mere artefact. Heightened interoceptive sensitivity (Domschke, Stevens, Pfleiderer, & Gerlach, 2010) and intolerance of uncertainty (Carleton, 2012) are characteristic of many patients with anxiety disorders and may enhance the likelihood of being diagnosed with a thyroid disorder via increased healthcare seeking. This squares well with observations that individuals with subclinical forms of hyperthyroidism differ in the extent to which they experience and report symptoms (Cooper & Biondi, 2012). However, this hypothesis is refuted by the fact that those studies diagnosing thyroid disorders through physical examinations and laboratory testing rather than by reviewing medical histories still found their presence significantly linked with anxiety disorders (Carta et al., 2004; Sareen et al., 2006). Moreover, there was evidence for concomitant anxiety and HPT alterations on a subclinical level (case-control and correlational studies), again rendering this an unlikely scenario. Another explanation is common risk factors. Regular smoking and nicotine dependence is substantial in anxiety disorders (Morissette, Tull, Gulliver, Kamholz, & Zimering, 2007) and at the same time significantly increases the likelihood of developing overt hyperthyroidism, as present in Graves' disease (Wiersinga, 2013). Against this, the two herein reviewed studies that controlled for smoking both still found the association between anxiety and thyroid dysfunction significant (Panicker et al., 2009; Sanna et al., 2013). Finally, there is the explanation of partly shared aetiopathogenetic mechanisms. Stress-related long-term alterations in the hypothalamic-pituitary-adrenal (HPA) axis are present in some patients with anxiety disorders (Elnazer & Baldwin, 2014) and may at the same time foster autoimmunity via shifting of the Th1/Th2 immune balance (Elenkov, 2008; Montoro et al., 2009). This is in line with evidence for psychosocial stress preceding the onset of Graves' disease, an autoimmune thyroid disorder (Bagnasco, Bossert, & Pesce, 2006). While the findings of the present review do not contradict this notion, they provide no direct support for it either. It is therefore upon future research to determine whether stress is indeed a contributor to the co-existence of anxiety and HPT abnormalities.

This is the first systematic review of the literature on HPT axis functioning in anxiety disorders. While we believe it useful in summarising the current state of research and outlining pitfalls and promises of future research, a number of limitations need to be considered. First, albeit comprehensive, our search yielded relatively few studies that matched the a priori defined eligibility criteria. This points out the need for further research in this somewhat neglected area. Second, there was substantial methodological heterogeneity. For instance, studies varied in their use of DSM-III-R versus DSM-IV criteria, which in terms of the present review means that the six epidemiological studies diagnosing GAD included slightly different patient populations. Heterogeneity was further increased by our decision to consider and combine evidence from different types of studies (comorbidity, case-control, and correlational). Considering this heterogeneity, we did not think it sensible to undertake a meta-analysis to determine the strength of the anxiety-thyroid dysfunction association. Third, while the HPT axis assessments were properly conducted in most studies, the risk of bias review also revealed a number of methodological limitations. For instance, despite excluding patients with a current major depressive episode, not all clinical studies assessed whether patients had a history of (hypo)manic episodes. Given the evidence for significant co-occurrence between PD and bipolar disorder (Vazquez, Baldessarini, & Tondo, 2014), and for HPT alterations in at least some patients with bipolar disorders (e.g., Barbuti et al., 2017; Kleiner et al., 1999), further case-control studies are advised to apply even more rigorous eligibility criteria. We also encourage future studies to systematically report the blinding of study personnel towards laboratory results and to rigorously control all statistical analyses for age, sex, BMI, smoking, and current levels of depression where applicable.

Taken together, the present review found the comorbidity between anxiety disorders and thyroid disorders was significant. This is supportive of the recommendation to routinely screen for thyroid disorders when treating patients with anxiety disorders (e.g., Bandelow et al., 2014). Half of the studies supported the notion of subclinical thyroid dysfunction in that TSH responses to TRH administration were blunted and an inverse relationship was observed between self-reported anxiety levels and TSH. It is tempting to speculate that in some patients, anxiety and thyroid dysfunction partly emanate from shared aetiopathogenetic factors, such as stress. However, the risk of bias assessment of this review clearly underscores the need for more high-quality studies prior to further investigation of

this issue. Case-control designs including patients with different forms of anxiety and depression, and potentially other stress-related disorders presenting with bodily symptoms (e.g., somatic symptom disorder), seem particularly promising in this respect. Furthermore, the use of laboratory challenges mimicking real-life psychosocial stress (e.g., the Trier Social Stress Test; Kirschbaum, Pirke, & Hellhammer, 1993) may prove an intriguing alternative to pharmacologically probing the HPT axis with standardised doses of exogenous TRH. We further believe that longitudinal epidemiological research is necessary at this stage to delineate the temporal order in which anxiety and (subclinical) thyroid disorders evolve over the course of development. Combining these approaches should allow for further progress to be made in unravelling the extent and meaning of thyroid dysfunction in anxiety disorders.

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References

APA. (1987). Diagnostic and Statistical Manual of Mental Disorders (3rd edition, revised). Washington DC: APA.

APA. (2000). Diagnostic and Statistical Manual of Mental Disorders (4th edition, text revision). Washington D.C.: APA.

APA. (2013). Diagnostic and Statistical Manual of Mental Disorders (5th edition). Washington D.C.: APA.

Bagnasco, M., Bossert, I., & Pesce, G. (2006). Stress and autoimmune thyroid diseases. Neuroimmunomodulation, 13, 309-317.

Balada, F., Torrubia, R., & Arque, J. M. (1992). Thyroid hormone correlates of sensation seeking and anxiety in healthy human females. Neuropsychobiology, 25, 208-213.

Bandelow, B., Wiltink, J., Alpers, G. W., Benecke, C., Deckert, J., Eckhardt-Henn, A., . . . M.E., B. (2014). Deutsche S3-Leitlinie Behandlung von Angststörungen. Retrieved from www.awmf.org/leitlinien.html

Barbuti, M., Carvalho, A. F., Köhler, C. A., Murru, A., Verdolini, N., Guiso, G., . . . Pacchiarotti, I. (2017). Thyroid autoimmunity in bipolar disorder: A systematic review. J Affect Disord, 221, 97-106.

Bauer, M., Goetz, T., Glenn, T., & Whybrow, P. C. (2008). The thyroid-brain interaction in thyroid disorders and mood disorders. J Neuroendocrinol, 20, 1101-1114.

Carleton, R. N. (2012). The intolerance of uncertainty construct in the context of anxiety disorders: theoretical and practical perspectives. Expert Rev Neurother, 12, 937-947.

Carta, M. G., Loviselli, A., Hardoy, M. C., Massa, S., Cadeddu, M., Sardu, C., . . . Mariotti, S. (2004). The link between thyroid autoimmunity (antithyroid peroxidase autoantibodies) with anxiety and mood disorders in the community: a field of interest for public health in the future. BMC Psychiatry, 4, 25.

Chaker, L., Bianco, A. C., Jonklaas, J., & Peeters, R. P. (2017). Hypothyroidism. Lancet.

Chiovato, L., Marino, M., Perugi, G., Fiore, E., Montanelli, L., Lapi, P., . . . Pinchera, A. (1998). Chronic recurrent stress due to panic disorder does not precipitate Graves' disease. J Endocrinol Invest, 21, 758-764.

Cleare, A., Pariante, C. M., Young, A. H., Anderson, I. M., Christmas, D., Cowen, P. J., . . . Members of the Consensus, M. (2015). Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines. J Psychopharmacol, 29, 459-525.

Cooper, D. S., & Biondi, B. (2012). Subclinical thyroid disease. Lancet, 379(9821), 1142-1154.

De Leo, S., Lee, S. Y., & Braverman, L. E. (2016). Hyperthyroidism. Lancet, 388, 906-918.

Domschke, K., Stevens, S., Pfleiderer, B., & Gerlach, A. L. (2010). Interoceptive sensitivity in anxiety and anxiety disorders: an overview and integration of neurobiological findings. Clin Psychol Rev, 30, 1-11.

Elenkov, I. J. (2008). Neurohormonal-cytokine interactions: implications for inflammation, common human diseases and well-being. Neurochem Int, 52, 40-51.

Elnazer, H. Y., & Baldwin, D. S. (2014). Investigation of cortisol levels in patients with anxiety disorders: a structured review. Curr Topics Behav Neurosci, 18, 191-216.

Fardella, C., Gloger, S., Figueroa, R., Santis, R., Gajardo, C., Salgado, C., . . . Foradori, A. (2000). High prevalence of thyroid abnormalities in a Chilean psychiatric outpatient population. J Endocrinol Invest, 23, 102-106.

Feldman, A. Z., Shrestha, R. T., & Hennessey, J. V. (2013). Neuropsychiatric manifestations of thyroid disease. Endocrinol Metab Clin North Am, 42, 453-476.

Fischer, S., & Cleare, A. J. (2017). Cortisol as a predictor of psychological therapy response in anxiety disorders-systematic review and meta-analysis. J Anxiety Disord, 47, 60-68.

Fischer, S., Strawbridge, R., Vives, A. H., & Cleare, A. J. (2017). Cortisol as a predictor of psychological therapy response in depressive disorders: systematic review and meta-analysis. Br J Psychiatry, 210, 105-109.

Fossey, M. D., Lydiard, R. B., Ballenger, J. C., Laraia, M. T., Bissette, G., & Nemeroff, C. B. (1993). Cerebrospinal fluid thyrotropin-releasing hormone concentrations in patients with anxiety disorders. J Neuropsychiatry Clin Neurosci, 5, 335-337.

Fountoulakis, K. N., Kantartzis, S., Siamouli, M., Panagiotidis, P., Kaprinis, S., Iacovides, A., & Kaprinis, G. (2006). Peripheral thyroid dysfunction in depression. World J Biol Psychiatry, 7, 131-137.

Giynas Ayhan, M., Uguz, F., Askin, R. & Gonen, M.S. (2014). The prevalence of depression and anxiety disorders in patients with euthyroid Hashimoto's thyroiditis: a comparative study. Gen Hosp Psychiatry, 36, 95-98.

Gloger, S., Fardella, C., Santis, R., & Bitran, J. (1997). Thyroid function assessment in psychiatric patients. Rev Med Chile, 125, 1351-1356.

Goldberg, D., Kendler, K. S., Sirovatka, P. J. & Regier, D. A. (2010). Diagnostic Issues in Depression and Generalised Anxiety Disorder. Refining the Research Agenda for DSM-V. Arlington, VA: APA.

Hofmann, P. J., Nutzinger, D. O., Kotter, M. R., & Herzog, G. (2001). The hypothalamic-pituitary-thyroid axis in agoraphobia, panic disorder, major depression and normal controls. J Affect Disord, 66, 75-77.

Kikuchi, M., Komuro, R., Oka, H., Kidani, T., Hanaoka, A., & Koshino, Y. (2005). Relationship between anxiety and thyroid function in patients with panic disorder. Prog Neuropsychopharmacol Biol Psychiatry, 29, 77-81.

Kim, T. H., Kim, K. W., Ahn, H. Y., Choi, H. S., Won, H., Choi, Y., . . . Park, Y. J. (2013). Effect of seasonal changes on the transition between subclinical hypothyroid and euthyroid status. J Clin Endocrinol Metab, 98, 3420-3429.

Kirschbaum, C., Pirke, K. M., & Hellhammer, D. H. (1993). The 'Trier Social Stress Test'--a tool for investigating psychobiological stress responses in a laboratory setting. Neuropsychobiology, 28, 76-81.

Kleiner, J., Altshuler, L., Hendrick, V. & Hershman, J. M. (1999). Lithium-induced subclinical hypothyroidism. Review of the literature and guidelines for treatment. J Clin Psychiatry, 60, 249-255.

Montoro, J., Mullol, J., Jauregui, I., Davila, I., Ferrer, M., Bartra, J., . . . Valero, A. (2009). Stress and allergy. J Investig Allergol Clin Immunol, 19, 40-47.

Morissette, S. B., Tull, M. T., Gulliver, S. B., Kamholz, B. W., & Zimering, R. T. (2007). Anxiety, anxiety disorders, tobacco use, and nicotine: A critical review of interrelationships. Psychol Bull, 133, 245-272.

Noyes, R., Jr., Woodman, C., Garvey, M. J., Cook, B. L., Suelzer, M., Clancy, J., & Anderson, D. J. (1992). Generalized anxiety disorder vs. panic disorder. Distinguishing characteristics and patterns of comorbidity. J Nerv Ment Dis, 180, 369-379.

Panicker, V., Evans, J., Bjoro, T., Asvold, B. O., Dayan, C. M., & Bjerkeset, O. (2009). A paradoxical difference in relationship between anxiety, depression and thyroid function in subjects on and not on T4: findings from the HUNT study. Clin Endocrinol (Oxf), 71, 574-580.

Patten, S. B., Williams, J. V., Esposito, E., & Beck, C. A. (2006). Self-reported thyroid disease and mental disorder prevalence in the general population. Gen Hosp Psychiatry, 28, 503-508.

Roberts, L. M., Pattison, H., Roalfe, A., Franklyn, J., Wilson, S., Hobbs, F. D., & Parle, J. V. (2006). Is subclinical thyroid dysfunction in the elderly associated with depression or cognitive dysfunction? Ann Inter Med, 145, 573-581.

Rogers, M. P., White, K., Warshaw, M. G., Yonkers, K. A., Rodriguez-Villa, F., Chang, G., & Keller, M. B. (1994). Prevalence of medical illness in patients with anxiety disorders. Int J Psychiatry Med, 24, 83-96.

Russell, W., Harrison, R. F., Smith, N., Darzy, K., Shalet, S., Weetman, A. P., & Ross, R. J. (2008). Free triiodothyronine has a distinct circadian rhythm that is delayed but parallels thyrotropin levels. J Clin Endocrinol Metab, 93, 2300-2306.

Sanna, L., Stuart, A. L., Pasco, J. A., Kotowicz, M. A., Berk, M., Girardi, P., . . . Williams, L. J. (2013). Physical comorbidities in men with mood and anxiety disorders: a population-based study. BMC Med, 11, 110.

Sareen, J., Jacobi, F., Cox, B. J., Belik, S. L., Clara, I., & Stein, M. B. (2006). Disability and poor quality of life associated with comorbid anxiety disorders and physical conditions. Arch Intern Med, 166, 2109-2116.

Simon, N. M., Blacker, D., Korbly, N. B., Sharma, S. G., Worthington, J. J., Otto, M. W., & Pollack, M. H. (2002). Hypothyroidism and hyperthyroidism in anxiety disorders revisited: new data and literature review. J Affect Disord, 69, 209-217.

Stein, M. B., Muir-Nash, J., & Uhde, T. W. (1991). The QKd interval in panic disorder: an assessment of end-organ thyroid hormone responsivity. Biol Psychiatry, 29, 1209-1214.

Stein, M. B., & Uhde, T. W. (1991). Endocrine, Cardiovascular, and Behavioral-Effects of Intravenous Protirelin in Patients with Panic Disorder. Arch Gen Psychiatry, 48, 148-156.

Tak, L. M., Cleare, A. J., Ormel, J., Manoharan, A., Kok, I. C., Wessely, S., & Rosmalen, J. G. M. (2011). Meta-analysis and meta-regression of hypothalamic-pituitary-adrenal axis activity in functional somatic disorders. Biol Psychol, 87, 183-194.

Tancer, M. E., Stein, M. B., Gelernter, C. S., & Uhde, T. W. (1990). The hypothalamic-pituitary-thyroid axis in social phobia. Am J Psychiatry, 147, 929-933.

Tukel, R., Kora, K., Hekim, N., Oguz, H., & Alagol, F. (1999). Thyrotropin stimulating hormone response to thyrotropin releasing hormone in patients with panic disorder. Psychoneuroendocrinology, 24, 155-160.

Vazquez, G. H., Baldessarini, R. J., & Tondo, L. (2014). Co-occurrence of anxiety and bipolar disorders: clinical and therapeutic overview. Depress Anxiety, 31, 196-206.

WHO. (1992). The ICD-10 Classification of Mental and Behavioural Disorders - Clinical Descriptions and Diagnostic Guidelines. Geneva: World Health Organization.

Wiersinga, W. M. (2013). Smoking and thyroid. Clin Endocrinol (Oxf), 79, 145-151.

Witthauer, C., Ajdacic-Gross, V., Meyer, A. H., Vollenweider, P., Waeber, G., Preisig, M., & Lieb, R. (2016). Associations of specific phobia and its subtypes with physical diseases: an adult community study. BMC Psychiatry, 16, 155.

Table legends

Table 1 Quality rating scale to assess risk of bias in studies investigating the relationship between hypothalamic-pituitary-thyroid (HPT) functioning and anxiety (disorders); items modified from Tak et al. (2011), Fischer and Cleare (2017), and Fischer et al. (2017)

Table 2 Characteristics of included studies assessing the prevalence of thyroid disorders in patients with anxiety disorders (comorbidity studies)

Table 3 Characteristics of included studies measuring thyroid parameters in patients with anxiety disorders and controls (case-control studies)

Table 4 Characteristics of included studies measuring anxiety levels and thyroid parameters (correlational studies)

Table 1 Quality rating scale to assess risk of bias in studies investigating the relationship between hypothalamic-pituitary-thyroid (HPT) functioning and anxiety (disorders); items modified from Tak et al. (2011), Fischer and Cleare (2017), and Fischer et al. (2017)

1) What eligibility criteria were used?	*Non-clinical samples:* Representative sample of the general population (2) Community or primary care sample (0)
	Clinical samples: Regulated iodine intake, no comorbidity with major somatic diseases, no comorbidity with major mental disorders, no current medication use, 3-4 used (2) Regulated iodine intake, no comorbidity with major somatic diseases, no comorbidity with major mental disorders, no current medication use, 1-2 used (1) Regulated iodine intake, no comorbidity with major somatic diseases, no comorbidity with major mental disorders, no current medication use, 0 used or not clearly stated (0)
2) If applicable: How were controls recruited?	From the same population as patients (2) From a selected population, such as hospital staff or students, or not clearly stated (0)
3) How were thyroid disorders diagnosed or how were HPT measures taken?	*Thyroid disorders:* Diagnosis based on established cut-off values (2) Medical history/interview (1) Self-reported diagnosis (0)
	HPT measures: HPT measure adequate regarding time of day, storage conditions, type of assay, intra- and inter-assay variance, 3-4 fulfilled (2) HPT measure adequate regarding time of day, storage conditions, type of assay, intra- and inter-assay variance, 1-2 fulfilled (1) HPT measure adequate regarding time of day, storage conditions, type of assay, intra- and inter-assay variance, 0 fulfilled or not clearly stated (0)
4) How was the blinding implemented regarding HPT measures?	Assessor blind to case vs. control status or anxiety levels (2) Not blind or not clearly stated (0)
5) What confounders were used to	Age, sex, body mass index, smoking, depression, 4-5 stated (2)

adjust the statistical analyses?[a]	Age, sex, body mass index, smoking, depression, 2-3 stated (1) Age, sex, body mass index, smoking, depression, 0-1 or not clearly stated (0)

[a]In case of the variable being an exclusionary criterion or in case of no significant impact on statistical analyses, consider confounder as adjusted for

Table 2 Characteristics of included studies assessing the prevalence of thyroid disorders in patients with anxiety disorders (comorbidity studies)

Study	Sample	Anxiety disorder	Thyroid disorder	Main results	Quality assessment
Noyes et al. (1992)	N=112 (73 female, 39 male), mean age 42±12, n=41 generalised anxiety disorder, n=71 panic disorder Outpatient sample (USA) Inclusionary criteria: score > 18 on HRSA, ≥1 panic attack in the past 4 weeks (patients with panic disorder only) Exclusionary criteria: panic attacks (patients with generalised anxiety disorder only), psychosis, organic mental disorder, primary mood disorder, serious physical illness	Generalised anxiety disorder or panic disorder assessed by the SCID and HRSA	Medical history of thyroid disease	Prevalence of thyroid disorders in women with generalised anxiety disorder greater than in women with panic disorder	5/10
Rogers et al. (1994)	N=711 (471 female, 240 male), mean age 41±13	Current or past diagnosis of panic disorder, agoraphobia, generalised anxiety	Medical history of thyroid disease	Thyroid disease in 2% of male and 9% of female patients with panic disorder Prevalence of thyroid dysfunction only in	3/10

	Outpatient sample (USA) Inclusionary criteria: age >18 Exclusionary criteria: organic mental syndrome, schizophrenia, current psychosis	disorder, social phobia assessed by the SCID and SADS (results only available for panic disorder)		females with panic disorder greater than in the general population (literature controls)	
Gloger et al. (1997)	N=102 (74 female, 28 male), mean age 41±15, n=61 panic disorder (rest with depressive disorders) Outpatient sample (Chile) Exclusionary criteria: current medication use impacting on thyroid functioning	Panic disorder assessed by a clinical interview	TSH, T3, T4, fT4, TPO antibodies Hypothyroidism: TSH >10 µUl/ml; subclinical hypothyroidism: TSH 5-10 µUl/ml Hyperthyroidism: T3 >180 ng/dl and/or fT4 >1.8 ng/dl with TSH <0.1 µUl/ml Positive for TPO antibodies: ≥1:100 dilution Ultrasensitive chemiluminescence immunoassay and hemagglutination	Thyroid disorder in 39.3% of patients with panic disorder: 19.7% hypothyroidism (n=2 subclinical), 6.6% hyperthyroidism, 11.8% positive for TPO antibodies and/or goitre	3/8

Chiovato et al. (1998)	N=87, (70 female, 17 male), mean age 36 (range: 15-73) Outpatient sample (Italy) Exclusionary criteria: severe physical and laboratory abnormalities, current psychotic disorders, treatment with lithium/other drugs	Panic disorder assessed by the SCID	Family/personal history of thyroid disorders and physical examination	No history of hyperthyroidism in patients with panic disorder (hypothyroidism not reported), but small diffuse goitres present in 18.3%	2/8
Fardella et al. (2000)	N=268 (204 female, 64 male), mean age 38±14, n=28 panic disorder, n=28 panic disorder with major depressive disorder (rest with depressive disorder) Outpatient sample (Chile) Exclusionary criteria: major medical disease, comorbid axis I major psychiatric disorder,	Panic disorder assessed by the SCID	TSH, fT4, TPO antibodies Hypothyroidism: TSH > 10µUl/ml; subclinical hypothyroidism: TSH 5-10µUl/ml Hyperthyroidism: fT4 > 1.4, TSH suppressed plus radioiodine uptake > 20% Positive for TPO antibodies: ≥1:100 dilution	No presence of hypothyroidism in patients with panic disorder only (only n=1 subclinical), but 7.1% with hyperthyroidism and 21.4% were positive for TPO antibodies	5/8

	intake of lithium, carbamazepine, or oral contraceptives (past 6 months)		Automated chemiluminescence immunoassay and microhemagglutination		
Simon et al. (2002)	N=169 (93 female, 76 male), mean age 37±10 Outpatient sample (USA) Inclusionary criteria: age 18-65 Exclusionary criteria: pregnancy, lactation, unstable medical illness, substance abuse, psychosis, bipolar disorder, OCD, PTSD, personality disorder, intake of psychotropic medication, history of hypersensitivity to study drug, ongoing psychotherapy for anxiety disorder	Panic disorder, social phobia, generalised anxiety disorder assessed by the SCID or MINI	Medical history of thyroid disease Serum TSH, T3, T4 Hypothyroidism: TSH >10 mU/l plus abnormal T3 and/or T4 Hyperthyroidism: undetectable TSH plus abnormal T3 and/or T4 Sensitive assays	Previously diagnosed or newly established thyroid disorder in 2.2% of patients with panic disorder, 4.2% of patients with social phobia, 10.4% of patients with generalised anxiety disorder Prevalence of thyroid dysfunction only in generalised anxiety disorder greater than in the general population (literature controls)	4/10
Carta et al. (2004)	N=127 (79 female, 48 male) Community sample	Anxiety disorders assessed by simplified version of the CIDI	Serum TSH, fT3, fT4, TPO antibodies Positive for TPO	Only lifetime anxiety disorders not otherwise specified associated with being positive for TPO antibodies (other thyroid parameters	3/8

	(Sardinia)		antibodies: ≥20 IU/ml Chemiluminescent assay, chromatographic method, radioimmunoassay, echography	not reported)	
Sareen et al. (2006), see also Study I by Witthauer et al. (2016)	N=4181 (2268 female, 1913 male), age range 18-65 General population sample (Germany) Inclusionary criteria: age range 18-79 Exclusionary criteria: hospitalised, not fluent in German	Anxiety disorders assessed by the Munich CIDI	Physical examination, laboratory testing	Past-month anxiety disorder associated with increased likelihood of past-month thyroid disease	4/8
Sanna et al. (2013)	N=942 (all male), mean age 59 (range: 46-73) Population-based sample (Australia) Inclusionary criteria: male, age 20-97	Anxiety disorders assessed by the SCID	Self-reported medical history, confirmed by medical records, medication use or clinical data where possible	Lifetime anxiety disorder associated with increased likelihood of lifetime thyroid disease	3/8

Witthauer et al. (2016), Study I see also Sareen et al. (2006)	Two studies (original and replication study): Study I: N=4181 (2268 female, 1913 male), age range 18-65 General population sample (Germany) Inclusionary criteria: age range 18-79 Exclusionary criteria: hospitalised, not fluent in German Study II: N=3691 (1961 female, 1730 male), mean age 51 Community sample (Switzerland) Inclusionary criteria: age 35-75, Caucasian	Study I: specific phobia assessed by the Munich CIDI Study II: specific phobia assessed by the SADS	Study I: self-reported questionnaire and medical interview by physician Study II: medical part of psychiatric interview	Study I: Specific phobia in the past 12 months associated with increased likelihood of lifetime thyroid disease Study II: Specific phobia in the past 12 months not associated with increased likelihood of lifetime thyroid disease	2/8

CIDI = Composite International Diagnostic Interview
MINI = Mini International Neuropsychiatric Interview
OCD = obsessive-compulsive disorder
HRSA = Hamilton Rating Scale for Anxiety
HSCL = Hopkins Symptom Checklist
PTSD = posttraumatic stress disorder
SADS = Schedule for Affective-Disorders and Schizophrenia

SCID = Structured Clinical Interview for DSM-IV
SCL-90 = Symptom Checklist-90
T3 = triiodothyronine
T4 = thyroxine
TPO = thyroid peroxidase
TSH = thyroid stimulating hormone

Table 3 Characteristics of included studies measuring thyroid parameters in patients with anxiety disorders and controls (case-control studies)

Study	Sample	Anxiety disorder	Thyroid measure	Main results	Quality assessment
Tancer, Stein, Gelernter, and Uhde (1990)	Three sub-studies with overlapping patients: Study I: N=52 (30 female, 22 male), mean age 37±12, n=26 patients, n=26 healthy controls Study II: N=35 (20 female, 15 male), mean age 35±10, n=13 patients, n=22 healthy controls Study III: N=86 (54 female, 32 male), mean age 34±10, n=43 patients, n=43 healthy controls Outpatient samples (USA) Exclusionary criteria: medical illness, history of thyroid disease,	Social phobia assessed by the ADIS	Study I: plasma TSH, T3, T4, fT4 Study II: TRH (500 μg) challenge from 9-10 am: TSH measured at -15 min, 0 min, +15 min, +30 min, +45 min Study III: Tg antibodies, TPO antibodies at 4 pm Radioimmunoassay, equilibrium dialysis, indirect hemagglutination, tanned red cell method	Study I: No differences in thyroid parameters between patients with social phobia and controls Study II: No differences in resting TSH between patients and controls, and no differences in responses in general, but patients more frequently showed blunted TSH responses when using a cut-off of either 5 or 7 μIU/ml Study III: No differences in antibody titres between patients and controls	6/10

	major depression, intake of (thyroid) medication				
Stein, Muir-Nash, and Uhde (1991)	N=35 (19 female, 16 male), mean age 32±6, n=15 patients, n=20 healthy controls Psychiatric sample (USA) Exclusionary criteria: physical illnesses, medication use (past 2 weeks)	Panic disorder according to DSM-III-R criteria	Plasma TSH, T3, T4, fT4	No differences in thyroid parameters between patients with panic disorder and controls	3/10
Stein and Uhde (1991)	N=48 (29 female, 19 male), mean age 35±9, n=26 patients, n=22 healthy controls Mixed outpatient (n=21) and inpatient (n=5) sample (USA) Exclusionary criteria: history of thyroid disease, physical illnesses, current major depression, medication	Panic disorder assessed by the SADS	TRH (500 μg) challenge at 9 am: TSH measured at 0 min, +15 min, +30 min, +45 min, +60 min Immunoradiometric assay	No differences in resting and stimulated TSH between patients with panic disorder and controls, and no differences regarding the frequency of blunted TSH responses when using a cut-off of 7µU/ml	6/10

	use (past 2 weeks)				
Fossey et al. (1993)	N=56 (31 female, 25 male), mean age 35±10, n=45 patients, n=11 healthy controls USA Exclusionary criteria: major depression (only included when anxiety preceded onset of major depression), current axis I disorder, current medication use	Panic disorder, generalised anxiety disorder, obsessive-compulsive disorder assessed by the SCID	Cerebrospinal TRH at 8-10 am Radioimmunoassay	No differences in TRH between patients with an anxiety disorder and controls	4/10
Chiovato et al. (1998)	N=349, mean age 36 (range: 15-73), n=87 patients, n=262 healthy controls Outpatient sample (Italy) Exclusionary criteria: severe physical and laboratory abnormalities, current psychotic disorders, treatment with	Panic disorder assessed by the SCID	Serum TSH, fT3, fT4, Tg antibodies, TPO antibodies, TR antibodies Ultrasensitive immunoradiometric assay, radioimmunoassay	No difference in the amount of detected antibodies between patients with panic disorder and controls (no other parameters reported)	4/10

	lithium/other drugs				
Tukel, Kora, Hekim, Oguz, and Alagol (1999)	N=30 (14 female,16 male), mean age 34±8, n=15 patients, n=15 healthy controls Turkey Exclusionary criteria: past or current organic disorder, current major depressive episode, intake of medication (past 2 weeks)	Panic disorder assessed by the SCID	TRH (400 μg) challenge at 9 am: serum TSH measured at 0 min, +15 min, +30 min, +60 min Chemiluminescent immunoassay	No differences in resting TSH between patients with panic disorder and controls Blunted TSH response in patients when compared to controls Patients more frequently showed blunted TSH responses when using a cut-off of 5 μIU/ml, but not when using a cut-off of 7 μIU/ml	6/10
Fardella et al. (2000)	N=268 (204 female, 64 male), mean age 38±14, n=28 panic disorder, n=28 panic disorder with major depressive disorder, n=168 major depressive disorder, n=44 bipolar disorder Outpatient sample (Chile) Exclusionary criteria: major medical disease,	Panic disorder assessed by the SCID	TSH, fT4, TPO antibodies Immunometric assay, chemiluminescence immunoassay, microhemagglutination	Patients with panic disorder had higher fT4 when compared to the other patient groups, while TSH did not differ across groups	6/10

	comorbid axis I major psychiatric disorder, intake of lithium, carbamazepine, or oral contraceptives (past 6 months)				
Hofmann, Nutzinger, Kotter, and Herzog (2001)	N=66 (33 female, 33 male), mean age 34±2.1, n=22 panic disorder, n=22 agoraphobia without history of panic disorder, n=22 healthy controls Outpatient sample (Austria) Exclusionary criteria: medical disease (including thyroid disorders), medication intake (past week)	Panic disorder or agoraphobia assessed by the SCID	TRH (400 μg) challenge at 8 am: serum TSH measured at 0 min, +20 min, +30 min, +40 min Radioimmunoassay (microparticle-enzyme-immunoassay)	Blunted TSH response in patients with panic disorder when compared to controls (resting TSH not reported) No difference between patients with agoraphobia and controls No differences across the three groups regarding the frequency of blunted TSH responses when using a cut-off of either 5µU/ml or 7µU/ml	8/10
Kikuchi et al. (2005)	N=66 (37 female, 29 male), mean age 34 (range: 16-75), n=46 panic disorder with agoraphobia, n=20 panic disorder without	Panic disorder with/without agoraphobia according to DSM-IV criteria	TSH, fT3, fT4 between 10 am and 2 pm Enzyme immunoassay	Medicated patients (probably antidepressants) with combined panic disorder and agoraphobia had higher fT3 when compared to those with panic disorder only, while no differences emerged in unmedicated patients	6/10

	agoraphobia Outpatient sample (Japan) Exclusionary criteria: history of endocrine, cardiovascular, respiratory, hepatic or renal disease, TSH outside of normal range, history of other psychiatric disorders	

ADIS = Anxiety Disorder Interview Schedule
DSM = Diagnostic and Statistical Manual of Mental Disorders
FSS = Fear Survey Schedule-II
SADS = Schedule for Affective Disorders and Schizophrenia
SCID = Structured Clinical Interview for DSM
STAI = State-Trait Anxiety Inventory
T3 = triiodothyronine
T4 = thyroxine
Tg = thyroglobulin
TPO = thyroid peroxidase
TRH = thyroid releasing hormone
TSH = thyroid stimulating hormone

Table 4 Characteristics of included studies measuring anxiety levels and thyroid parameters (correlational studies)

Study	Sample	Anxiety measure	Thyroid measure	Main results	Quality assessment
Stein and Uhde (1991)	N=48 (29 female, 19 male), mean age 35±9, n=26 patients, n=22 healthy controls Mixed outpatient (n=21) and inpatient (n=5) sample (USA) Exclusionary criteria: history of thyroid disease, current major depression, medication use (past 2 weeks)	Panic disorder assessed by the SADS Anxiety (Sheehan Patient-Rated Anxiety Scale, STAI, ZAS)	TRH (500 μg) challenge at 9 am: TSH measured at 0 min, +15 min, +30 min, +45 min, +60 min Immunoradiometric assay	No correlation between anxiety levels and TSH	3/8
Balada et. al (1992)	N=37 (37 female), mean age 31 ± 6 Family planning unit (Spain) Inclusionary criteria: normal menstrual cycle Exclusionary criteria:	Anxiety (STAI)	TSH, T3 and T4 between 9.30 and 10.30 am Radioimmunoassay	Anxiety levels not associated with thyroid parameters	3/8

	history of alcohol or drug abuse, endocrine or serious somatic illness, medication intake, oral contraceptive intake (past 6 months)				
Fossey et al. (1993)	N=56 (31 female, 25 male), mean age 35±10, n=45 patients, n=11 healthy controls USA Exclusionary criteria: major depression (only included when anxiety preceded onset of major depression), current axis I disorder, current medication use	Panic disorder, generalised anxiety disorder, or obsessive-compulsive disorder assessed by the SCID Anxiety (Clinician-Rated Anxiety Scale, HRSA, SCL-90)	Cerebrospinal TRH at 8-10 am Radioimmunoassay	No association between any anxiety measure and TRH	3/8
Tukel et al. (1999)	N=30 (14 female,16 male), mean age 34±8, n=15 patients, n=15 healthy controls Turkey Exclusionary criteria: past or current organic	Panic disorder assessed by the SCID Anxiety (HRSA)	TRH (400 μg) challenge at 9 am: serum TSH measured at 0 min, +15 min, +30 min, +60 min Chemiluminescent immunoassay	Anxiety levels negatively associated with TSH responses	3/8

	disorder, current major depressive episode, intake of medication (past 2 weeks)				
Kikuchi et al. (2005)	N=66 (37 female, 29 male), mean age 34 (range: 16-75) Outpatient sample (Japan) Exclusionary criteria: history of endocrine, cardiovascular, respiratory, hepatic or renal disease, TSH outside of normal range, history of other psychiatric disorders	Panic disorder with/without agoraphobia according to DSM-IV criteria Anxiety (STAI)	TSH, fT3, fT4 between 10 am and 2 pm Enzyme immunoassay	Anxiety levels negatively associated with fT4 in unmedicated patients (probably antidepressants), no significant correlation between hormone levels and anxiety level in medicated patients	3/8
Roberts et. al (2006)	N=5868 (2985 female, 2883 male), mean age 73 ± 6 Primary care sample (United Kingdom) Inclusionary criteria: age >65 years Exclusionary criteria:	Depression and anxiety (HADS)	Serum TSH, fT4, fT3 (only when TSH or fT4 abnormal) Chemiluminescent immunoassay	Anxiety levels negatively associated with TSH, but not with fT4	2/8

	diagnosis of thyroid disease, current or past thyroid treatment (12 months)				
Panicker et al. (2009)	N=28'400 (18'959 female, 9441 male), mean age 60±13 General population sample (Norway) Inclusionary criteria: age >40 Exclusionary criteria: use of psychotropic medication, history of thyroid but not on T4	Anxiety (HADS)	Blood TSH Ultrasensitive immunoradiometric assay	Negative association between anxiety levels and TSH in subjects with no known thyroid disease In women on T4 anxiety positively associated with TSH (not enough power to test men)	5/8

BSI = Brief Symptom Inventory – anxiety subscale
DSM = Diagnostic and Statistical Manual of Mental Disorders
HADS = Hospital Anxiety and Depression Scale
HRSA = Hamilton Rating Scale for Anxiety
MINI = Mini International Neuropsychiatric Interview
PHQ-9 = Patient Health Questionnaire – depression
SADS = Schedule for Affective Disorders and Schizophrenia
SCID = Structured Clinical Interview for DSM
SCL-90 = Symptom Checklist 90
STAI = State-Trait Anxiety Inventory
T3 = triiodothyronine
T4 = thyroxine
TRH = thyroid releasing hormone
TSH = thyroid stimulating hormone

Susanne Fischer

ZAS = Zung Anxiety Scale